

REMARKS

Status of the Claims

Claims 1-64 are currently pending in the application. Claims 7, 20 and 58 stand rejected. The Examiner objects to claims 7, 20 and 58. Claims 1-6, 8-19, 21-57 and 59-61 are withdrawn as being drawn to a non-elected invention. Claims 7, 20 and 58 have been amended as set forth herein without prejudice or disclaimer. New claims 62-64 have been added herein. No new matter has been added by way of the present amendments. Specifically, the amendments to claims 7 and 20 are supported by the specification at, for instance, page 84, second paragraph. Amendments to claim 58 are to conform the claim more closely to US practice. Support for new claims 62-64 may be found in the specification at, for instance, page 84. Reconsideration is respectfully requested.

Unity of Invention Requirement

For the purposes only of furthering prosecution, Applicants hereby affirm their election to prosecute the subject matter of Group II, claims 7, 20 and 58, with traverse. Applicants further affirm the selection of SEQ ID NO:2 as the initial species used for examination purposes, also with traverse. Applicants traverse the Unity of Invention requirement on the basis already made of record. It is understood that once allowable subject matter has been identified with respect to this species, additional species generic to the claims will be further considered. Additionally, it is understood that according to Unity of Invention standards, once allowable subject matter concerning Group II claims has been identified, additional subject may be rejoined.

Objections to the Claims

The Examiner objects to claims 7, 20 and 58. (*See*, Office Action of April 5, 2007, at page 3, hereinafter, "Office Action"). The Examiner states that claims 7, 20 and 58 encompass non-elected subject matter. Although Applicants do not agree that such amendments are required at this stage in prosecution, or at least until allowable subject matter is identified, to expedite prosecution, claim 7 has been amended herein without prejudice or disclaimer to recite, "An isolated and purified ectodomain fragment of AMIGO polypeptide comprising amino acids 1-371 of the amino acid sequence of SEQ ID NO:2, amino acid sequence of SEQ ID NO:4 or amino acid sequence of SEQ ID NO:6." Furthermore, claim 20 has been amended herein without prejudice or disclaimer to recite, "A pharmaceutical composition comprising amino acids 1-371 of SEQ ID NO:2 or an antibody specifically binding to amino acids 1-371 of SEQ ID NO:2." Claim 58 depends from claims 7 and 20 and thereby incorporates by reference all of the limitations of claims 7 and 20.

Therefore, reconsideration and withdrawal of the object to claims 7, 20 and 58 are respectfully requested.

Rejections Under 35 U.S.C. § 112, First Paragraph

Enablement

Claims 20 and 58 stand rejected under 35 U.S.C. § 112, first paragraph, for failing to comply with the enablement requirement. (*See*, Office Action, at page 3). Applicants traverse the rejection as set forth herein.

The Examiner states that the present specification enables one of ordinary skill in the art to enhance neurite outgrowth of hippocampal neurons that are cultured on plates coated with the extracellular domain of AMIGO. (*Id.* at page 5). The Examiner states that Applicants disclosure does not provide sufficient guidance on how to use the pharmaceutical composition of claim 20 to treat “all different diseases including different neurodegenerative diseases and neurological conditions that have different causes as described in the specification (see p. 47 & 49) since the soluble form of the extodomain of AMIGO has inhibitory effects on neurite outgrowth and fasciculation.” (*Id.*). The Examiner believes Applicants have not enabled one of ordinary skill in the art to practice the presently claimed invention including full length AMIGO and/or all fragments of AMIGO used to treat all neurological diseases. (*Id.*).

Although Applicants do not agree that claims 20 and 58 lack enablement support in the specification, to expedite prosecution, claim 20 has been amended herein without prejudice or disclaimer to recite as follows. “A pharmaceutical composition comprising amino acids 1-371 of SEQ ID NO:2 or an antibody specifically binding to amino acids 1-371 of SEQ ID NO:2.” This amendment is supported by the as-filed specification at, for instance, page 84. Briefly, according to the specification, a 1180-bp BamHI fragment encoding for the entire extracellular region of AMIGO was amplified by AMIGO nucleic acid specific primers. The 3' primer used is complementary to part of AMIGO nucleic acid encoding for the sequence between IG-domain and TM-domain. (*See*, Figure 2B of the specification). Exhibit 1, attached hereto, shows the actual site of complementary sequence for the 3' primer in mouse AMIGO1 nucleic acid sequence, i.e. nucleic acid positions 990 to 1108 of SEQ ID NO:13. This is exactly the same position as set forth by nucleotides 993 to 1111 of SEQ ID NO:1 encoding for human AMIGO1

polypeptide. Thus, the production of human AMIGO1 ectodomain consisting of 371 amino acids would have been within the abilities of a skilled artisan based on the present disclosure. (*See also*, Exhibit 2, alignment of murine and human AMIGO1, also attached hereto).

Applicants believe the presently amended claim 20 is fully enabled by the present specification because the specification fully discloses which diseases would be predicted to be treatable using the recited composition. (*See*, for instance, page 47, line 12 to page 49, line 33). Furthermore, the specification provides ample guidance to one of skill in the art, possessing all the knowledge of the state of the art, regarding how to administer the pharmaceutical composition of the presently claimed invention. For instance, beginning at page 50 and continuing to page 56, Applicants provide a wide-ranging disclosure detailing the knowledge of one of skill in the art and the capabilities known in the art for identification of subject in need of treatment and various modes of treatment.

Concerning pharmaceutical compositions specifically, Applicants assert that there is certainly a plethora of detailed disclosure provided in the as-filed specification teaching how to use the compositions of the presently claimed invention. For instance, beginning at page 56, sufficient guidance is provided concerning compositions of the present invention, their manufacture and formulations thereof.

The specification at page 60, line 7 continues with appropriate dosage amounts even providing specific amounts at lines 20-25. Even further, beginning at page 65, line 15 and continuing to page 67, line 12, additional embodiments of compositions of the presently claimed invention are disclosed.

Beginning at page 91, in the Examples section of the present specification, there is disclosed an regeneration experiment using AMIGO1, AMIGO2 or AMIGO3 proteins. This example is representative of the type of methodology that may employed in treating any such subject in need thereof using the compositions of the presently claimed invention. One of skill in the art can easily apply this example to any number of subjects suffering from related diseases.

Furthermore, although Applicants do not believe claim 58 lacks enablement support in the specification, to expedite prosecution, claim 58 has been amended without prejudice or disclaimer to recite as follows: "A method of treating diseases characterized by aberrant growth, migration, regeneration or proliferation of cells that express an AMIGO receptor, comprising administering to a subject in need thereof an effective amount of the composition according to claim 20."

Therefore, claim 58, at least as amended, is also fully enabled since the specification also provides detailed information on how to perform the method claimed. For instance, as already discussed, above, the specification fully discloses which diseases would be predicted to be treatable using the recited composition. (See, for instance, page 47, line 12 to page 49, line 33). Furthermore, the specification provided ample guidance to one of skill in the art, possessing all the knowledge of the state of the art, regarding how to administer the pharmaceutical composition of the presently claimed invention.

Additionally, the specification at, for instance, page 61, discloses inhibition of the function of EGFR. One of ordinary skill in the art is capable of determining which diseases may be treated by use of the presently claimed compositions for the inhibition of EGFR, and which diseases are "characterized by aberrant growth, migration, regeneration or proliferation of cells

that express an AMIGO receptor.” One of skill in the art certainly knows how to construct an antibody which can detect AMIGO receptor and thereby determine which diseases are characterized by aberrant growth, migration, regeneration or proliferation of cells expressing this receptor. In fact, the present specification, at pages 42-46 disclose a myriad known methods and uses for antibodies according to the present invention. This, combined with the knowledge of one of skill in the art certainly enables one of skill in the art to practice the full scope of the presently claimed invention as recited, for instance, in amended claim 58. (*See*, specification also beginning at page 61, entitled “USES OF AMIGO COMPOUNDS” for further disclosure of guidance on how to conduct the methods of the presently claimed invention). For instance, page 84 of the present specification, in the Examples section, discloses how an antibody against AMIGO was actually generated and tested empirically.

The Examiner is respectfully invited to read pages 91-103 of the specification, disclosing numerous examples of the successful application of compositions of the present invention in numerous contexts and models mimicking the diseases encompassed by the present claims. Applicants strongly assert that one of skill in the art, in light of this voluminous disclosure, would be fully enabled to practice (make and use) the presently claimed invention exactly as recited in the presently amended claims. If the Examiner disagrees, the Examiner is requested to state specifically which aspects of the presently claimed invention are believed to lack enablement.

The Examiner additionally alleges that the claims are not enabled due lack of knowledge of the “route, duration and quantity of administration of the claimed pharmaceutical composition.” (*See*, Office Action, at page 6). However, in light of the abundant disclosure of

the present specification and numerous examples provided, it is well within the abilities of one of ordinary skill in the art to determine these variables without undue experimentation.

Reconsideration and withdrawal of the enablement rejection of claims 20 and 58 are respectfully requested.

Written Description

Claims 20 and 58 stand rejected under 35 U.S.C. § 112, first paragraph, for failing to comply with the written description requirement. (*See*, Office Action, at page 9). Applicants traverse the rejection as set forth herein.

The Examiner's statements in this rejection appear to focus on the "broad genus of other polypeptides related to SEQ ID NO:2" encompassed by the claims. (*Id.*). Although Applicants do not agree that claims 20 and 58 lack written description support, to expedite prosecution, these claims have been amended herein without prejudice or disclaimer to recite, in part, "amino acids 1-371 of SEQ ID NO:2 or an antibody specifically binding to amino acids 1-371 of SEQ ID NO:2."

Reconsideration and withdrawal of the written description rejection of claims 20 and 58 are respectfully requested.

Rejections Under 35 U.S.C. § 102(b)

Claims 7, 20 and 58 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Shimkets et al., WO 00/70046 (hereinafter referred to as "Shimkets et al."). (*See*, Office Action, at page 13). Applicants traverse the rejection as set forth herein.

The Examiner states that Shimkets et al. disclose a sequence which is 100% identical to SEQ ID NO:2 of the presently claimed invention. (*Id.*). The examiner states that “intended use in treating diseases as recited in claims 20 and 58 are not given patentable weight since the claimed polypeptide does not result in a structural difference between the claimed invention and the prior art.” (*Id.*).

However, Shimkets et al. do not disclose any function for AMIGO1. That is, a functional AMIGO1 peptide fragment consisting of residues 1-371 of SEQ ID NO:2 cannot be anticipated by Shimkets et al. since Shimkets et al. do not ascribe any functional or structural importance to this region of SEQ ID NO:2. The ectodomain fragment of AMIGO1 is also advantageous over the entire sequence of SEQ ID NO:2 since the transmembrane domain in an isolated AMIGO1 polypeptide has little known use and would only hamper the use of the isolated AMIGO1 in therapeutic applications or laboratory assays. Furthermore, the presence of the transmembrane domain of AMIGO1 may make the production or secretion of a recombinant AMIGO1 polypeptide more difficult, since the transmembrane domain of AMIGO1 may interact with the membrane structures of the host cell.

In contrast, Applicants herein disclose and ascribe specific, important and useful biological function to the ectodomain fragment of AMIGO1 alone for the first time. Such features of AMIGO1 are not disclosed in Shimkets et al.

Shimkets et al. do not disclose this limitation anywhere in their application. Therefore, Shimkets et al. cannot anticipate the presently amended claims 7, 20 and 58. “A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or

inherently described, in a single prior art reference.” (See, *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987)).

Reconsideration and withdrawal of the anticipation rejection of claims 7, 20 and 58 are respectfully requested.

CONCLUSION

If the Examiner has any questions or comments, please contact Thomas J. Siepmann, Ph.D., Registration No 57,374, at the offices of Birch, Stewart, Kolasch & Birch, LLP.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to our Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under § 1.17; particularly, extension of time fees.

Dated: August 6, 2007

Respectfully submitted,



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Attachments: Exhibit 1 – Mouse AMIGO ectodomain cloning scheme
Exhibit 2 – Alignment of Murine and Human AMIGO1

Figure 1. Mouse AMIGO ectodomain cloning scheme

BamHI
5'CGGGATCCTAGGGTGACTCTCTCCAGATCC 3'

1 GCATCCTCGCCGAGCAGAACATGCCGGGGTGACTCCCTCCAGATCCTGTGGCCCTTCTCT

61 GCTCTTCCCACTGACACTATGCAACCCAGCGTACCTGCGAGGCGCTCTGGCTCTCTGCTG
M Q P O R D L R G L W L L L L

121 CTCTCCGTGTTCTCTGCTTCTCTTTGAGGTAGCCAGGCGCGGCCGATCTGTGGTGTAGTTGT
L S V F L L L F E V A R A G R S V V S C

181 CCCGCCAATCGTCTGTGCGCCAGCAACATCCTCAGCTGCTCCAAGCAGCAGCTGCCCAAT
P A N C L C A S N I L S C S K Q O L P N

241 GTGCCCAATCTTTGCCAGCTACACAGCACTGCTGGACCTCAGCCACACCACTTGAGC
V P Q S L P S Y T A L L D L S H N N L S

301 AGGCTCGGGCCGAGTGGACCCCAACCGGCTGACCAACCTGCACCTCCCTGCTGCTGAGC
R L R A E A W T P T R L T N L H S L L L S

361 CACAACCACTGAACCTCATCTCCTCCGAGGCGCTTCGCCCCGTACCCCACTAGGTAC
H N H L N F I S S E A F V P V P N L R Y

421 TTGGACCTCTCTCCCAACCATCTTCACACGCTGGATGAGTTCTGTTTCAGCGACCTGCAG
L D L S S N H L H T L D E F L F S D L Q

481 GCGCTGGAAGTCTGTGTCTTACAAATACCAATGTGTGGTGGTGGACCGGAATGCCCTTT
A L E V L L L Y N N H I V V V D R N A F

541 GAGGACATGGCCAGCTGCAGAACTCTACTTTRAGCCAGAATCAGATCTCTCGCTTTCTCT
E D M A Q L Q K L Y L S Q N Q I S R F F

601 GTGGAATGATCAAGGATGGGAACAAATTACCCAACTGATGCTCTTGGATCTGTCTCTCC
V E L I K D G N K L P K L M L D L S L

661 AACAGCTCAAGAAGTGTGCCCTGACTGACCTGCAGAAATTGCCAGCCTGGGTCAAGAAT
N K L K K L P L T D L Q K L P A W V K N

721 GGGCTATACCTGCATAACAACCCCTTGGAGTGGCACTGCAAGCTCTACAGCACTCTTTTCG
G L Y L H N N P L E C D C K L Y Q L F S

781 CACTGCGAGTACCGGAGCTGAGCTCTGTGATGGAATCCAGGAGGACCTGATCTGCATG
H W Q Y R Q L S S V M D F Q E D L Y C M

841 CACTCCAAGAAGCTGCACAACATCTTCAGCCTGGATTTCTTCAATTGCAGCGAGTAGAAG
H S K K L H N I F S L D F E N C S E Y K

901 GAAAGTGCTGGGAGGCTCACCTGGGAGACACCTTGACCATCAGGTGTGACACCAAAACAG
E S A W E A H L G D T L T I R C D T K Q

961 CAAGGATGACCAAGTGTGGGTGTCCCAAGCAATGAACAGGTGCTAAGTCAGGGGTCC
Q G M T K V W V S P S N E Q V L S Q G S

1021 AATGGCTCGGGTGGCGTGGGAATGGCACTTTTAAAAAGGTGCAGGTGCAGGAT
N G S V S V R N G D L F F K K V Q V E D

1081 GGGGTGTGTATACCTGTTACGCCATGGGGGAGACTTCAACGAGACACTGCTGTGGAG
G G V Y T C Y A M G E T F N E T L S V E

BamHI
3'CCTGTGGTACTGTGGGAGTTGCCTAGGGC 5'

1141 TTGAAAGTGATTAACCTTCACCTTGCACGGACACCATGACACCTCAACACAGCCTACACT
L K V Y N F T L H G H H D T L N T A Y T

1201 ACCCTGGTGGGCTGTATCTCTCAGTGTGGTTCTGGTCCTCATATACCTTGACTCACCCTT
T L V G C I L S V V L V L I Y L Y L T P

1261 TGCCGCTGCTGGTGTGGGGGTGTGGAGAACTTCCAGCCACCAAGGAGATAGCCTCAGC
C R C W C R G V E K P S S H O G D S L S

1321 TCTTCIATGCTCAGTACACACCAACCAAGCACCCTATGGCTGGTGGGGACAAGATGAT
S S M L S T T P N H D P M A G D G D K D D

1381 GGTTTTGACCGGGGGTGGCCCTTCTGGAACCTGCTGGACCGGGGAGGGTCAAAATGGC
G F D R R V A F L E P A G P G Q G Q N G

1441 AAACCTCAAGCCAGGCAACACTCTGCCGGTCCCGAAGCTACAGCAAGGGCCACAGGAGG
K L K P G N T L P V P E A T G K G Q R R

1501 ATGTCGATCCAGAGTCGGTCAGCTCGGTCTTTTCTGATACACCCACTGTGGTGTGAGCA
M S D P E S V S S V F S D T P I V V * A

Mouse AMIGO1 extracellular domain is underlined

Figure 2. Similarity of mouse AMIGO1 and human AMIGO1. Mouse and human AMIGO1 extracellular domain is underlined.

Mouse AMIGO1	1	<u>MQPQROLRGLWLLLSVFLLLFEVARAGRVS</u> VPSCPA CLCAS NTLSCSEKQQLPNVPSPLE	60
Human AMIGO1	1	<u>MEPRDRPRLWLLPSLSLLFEVARAGRVS</u> CPAAC LCAS NTLSCSEKQQLPNVPSPLE	60
similarity		M F RD RGLWLL S+ LLLFEVARAGR+VWSCPA CLCASNTLSCSEKQQLPNVP SLP	
Mouse AMIGO1	61	<u>SYTALLDLSHNNLSKLR</u> AEWTPTPLTNLHLLLSNNHLNFISSAEFSPVFNRLRYLDLSSN	120
Human AMIGO1	61	<u>SYTALLDLSHNNLSKLR</u> AEWTPTPLTQLHLLLSNNHLNFISSAEFSPVFNRLRYLDLSSN	120
similarity		SYTALLDLSHNNLSKLR AEWTPTPLT LHSLLLSNNHLNFISSAEF PVPNRLRYLDLSSN	
Mouse AMIGO1	121	<u>HLHTLDEFLEFSDIQLE</u> VLLLYNNHIVYVDNFAEDMAQLKLYLSQHQSIRFPVELIYD	180
Human AMIGO1	121	<u>QLRTLDEFLEFSDIQLE</u> VLLLYNNHIMAVDRCAFDDMAQLKLYLSQHQSIRFPVELIYK	180
similarity		L TLDEFLEFSDIQ LEVLLLYNNH+ VDR AF+DMAQLKLYLSQHQSIRFP+EL+K+	
Mouse AMIGO1	181	<u>GKLPKLMILLDLSSN</u> KKLPLTDLQKLPAMVKNGLYLHNNPLECCDKLYQLFSHWQYRQ	240
Human AMIGO1	181	<u>GAKLPKLTLLDLSSN</u> KKLNLPLDLQKLPAMIKNGLYLHNNPLNCCDKLYQLFSHWQYRQ	240
similarity		G KLPKL LLDLSSNKKL LPL DLQKLPAM+KNGLYLHNNPL CDC+LYQLFSHWQYRQ	
Mouse AMIGO1	241	<u>LSSVMDFQEDLYCM</u> HSKKLHNI FSLDF NCSEYKESAEAHGLGTLITRCDTKQQGMTEV	300
Human AMIGO1	241	<u>LSSVMDFQEDLYCM</u> HSKKLHNVFNL SFLNCG EYKERAEAHGLGTLITRCDTKQQGMTEV	300
similarity		LSSVMDFQEDLYCM+SKKLHN+F+L F NC EYKE AWEAHGLGTL I+CDTKQQGMTEV	
Mouse AMIGO1	301	<u>WYFSPNEQVLSQ</u> SGNSGVSV-RNGDLFFKKVQVEDGGVYTCYAMGETFNETLSVELKVYN	359
Human AMIGO1	301	<u>WYFSPNERVLDEVT</u> NGTVSVSGSL LFQGV QVELGGVYTCYAMGETFNETLSVELKVYN	360
similarity		V+FSNE+VL + +NG+VSV ++G L P++VQVEDGGVYTCYAMGETFNETLSVELKV+N	
Mouse AMIGO1	360	<u>FTLAGRHDTLNTAY</u> TTLVGCILSVVLVLIYLYLT PCRCWC RGVEFSSHQGDSLSSSMLS	419
Human AMIGO1	361	<u>FTLAGRHDTLNTAY</u> TTLVGCILSVVLVLIYLYLT PCRCWC RGVEFSSHQGDSLSSSMLS	420
similarity		FTLAGRHDTLNTAYTTLVGCILSVVLVLIYLYLT PCRCWC RGVEFSSHQGDSLSSSMLS	
Mouse AMIGO1	420	<u>TTFNHDP</u> MAGGDKDDGFD RRVAF LEFAGPGGGQNGRLKPGNTLPVPEATGKGQRMSDPE	479
Human AMIGO1	421	<u>TTFNHDP</u> MAGGDKDDGFD RRVAF LEFAGPGGGQNGRLKPGNTLPVPEATGKGQRMSDPE	480
similarity		TTFNHDPMAGGDKDDGFD RRVAF LEFAGPGGGQ+GKLEKPGNTLPVPEATGKGQRMSDPE	
Mouse AMIGO1	480	SVSSVFS DTPIV V 492	
Human AMIGO1	481	SVSSVFS DTPIV V 493	
similarity		SVSSVFS DTPIV V	

Mouse extracellular domain consists of amino acids 1 - 370

Human extracellular domain consists of amino acids 1 - 371